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The Hemostatic Effect of Adona (AC-17)

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Through the work of R o s k a m (1954) adrenochrome derivatives have been widely accepted as hemostatic agents, adrenoxyl adrenochrome monosemicarbazone sodium salicylate) being most commonly used. Favourable reports based on clinical experience have appeared [P e e l e (1958), R o l l a s o n (1958), R u d d e l l (1958)], but controlled clinical trials have failed to demonstrate conclusive effect [C a l n a n et I n n e s (1958), M a r c u s et S p a e t (1958), J e s p e r s e n (1959), S t o v n e r et B r e n n h o v d (1960)].

Japanese workers have recently prepared another adrenochrome derivative, Adona (AC-17), (sodium 1-methyl-5-semicarbazono-6-oxo-2,3,5,6-tetrahydroindole 3-sulfonate) (Tanabe Seiyaku Co., Ltd., Osaka, Japan). This preparation is claimed by the manufacturer to be 50 times more watersoluble than any other adrenochrome derivative, and it can therefore be injected intravenously in fairly large doses. It is supposed to reinforce capillaries without any effect on blood coagulation and platelets. The drug is chemically related to adrenalin, but has no effect on blood pressure, heart rate, respiration or blood sugar.

From Japan several favourable reports have appeared (see Summarized bibliography on Adona (AC-17), Tanabe Seiyaku Co., Ltd., Osaka, Japan). T h i e s (1958) found no effect on coagulation, but he observed a definite increase in capillary resistance, and recommended the drug in vascular hemorrhagic disorders. B u r k e et al. (1960) found that Adona (AC-17) significantly reduced the blood loss during prostatic surgery in patients with normal hemostatic mechanism.

The present investigation deals with the hemostatic effect of this drug in normal individuals, in patients with hemorrhagic diatheses, and in patients undergoing prostatic surgery.

Material

Adona (AC-17) for intravenous use, 5 mg/ml, was kindly supplied by Tanabe Seiyaku Co., Ltd., Osaka, Japan.

Methods

Routine tests of the hemostatic mechanism were carried out by standard procedures, see references in Table 1.

Table 1: Mean values in 10 normal individuals before, 30 minutes and 3 hours after an intravenous injection of 50 mg Adona (AC-17)

	Before	30 min after	3 hrs after	Normal values	Reference for methods
Bleeding time	6′ 6″	5′ 8″	6′ 11″	3—11′	Borchgrevink and Waaler, 1958
Whole blood clot time (min)	3	3	3½	2—5	Hjort and Stormorken, 1957
Tourniquet test* No. of petechiae	22	10	—	—	Stefanini and Dameshek, 1955
Thromboplastin time (sec)	15.0	15.0	15.1	14—16	Quick, with human thromboplastin
Cephalin time (sec)	64.7	64.5	65.6	60—70	Egeberg, 1961
P & P (%) (Proconvertin and prothrombin)	94	83	90	75—130	Owren and Aas, 1951
No. of platelets × 1000/cmm	284	268	270	150—400	Nygaard, 1933
Clot retraction (cm)					
after ½ hour	3.6	2.5	2.6		
after 1 hour	4.8	4 0	4.5		
after 2 hours	6.4	6.0	6.5		
after 3 hours	7.5	6.6	7.9	> 6	Voss, 1958

* The pressure was maintained for 10 minutes at 100 mm Hg.

Results

Normal individuals

Various hemostatic tests were carried out in normal individuals before, 30 minutes and 3 hours after an intravenous injection of 50 mg Adona (AC-17) (Table 1). The tourniquet test is normally negative, therefor, the pressure was maintained at 100 mm Hg for 10 minutes in order to provoke petecchiae even in normal individuals.

The drug had no effect on the four screening tests for the clotting mechanism, and also no effect on the platelet count. There was, however, a marked

effect on the number of petecchiae provoked by the tourniquet test 30 minutes after the injection. In 2 persons the number of petecchiae was reduced from 25 to 0, and from 60 to 5, respectively. In 4 persons there was a moderate reduction, and in 4 persons there was no effect.

The bleeding time was slightly shortened 30 minutes after the injection. In order to describe the bleeding more accurately, both duration of bleeding and the blood loss should be recorded. To measure the latter, the blood from the cuts of the bleeding time test was drawn into heparinized capillary tubes (80 mm × 1 mm). By measuring the length of the blood column, the blood loss was compared before and 30 minutes after an intravenous injection of 50 mg Adona (AC-17). Table 2 gives the result, the 100% value being the blood loss prior to injection. On an average, Adona (AC-17) reduced the blood loss by approximately one third.

Table 2: Blood loss during the bleeding time test in 10 normal persons 30 minutes after an intravenous injection of 50 mg Adona (AC-17). The blood loss is expressed as % of the blood loss during the same test prior to the injection

Person	Blood loss (%)
1	80
2	100
3	90
4	53
5	60
6	75
7	33
8	52
9	68
10	70
Average	68

Patients

11 patients with a prolonged bleeding time due to various causes received 50 mg Adona (AC-17) intravenously. The bleeding time was tested before and 30 minutes after the injection. Table 3 shows that no measurable change took place.

The same dose was given to 8 patients with a positive tourniquet test. It is seem from Table 4 that no effect could be demonstrated.

Prostatectomy

40 consecutive patients were operated by the method of Harris (1929) by the same team of surgeons [Andersen (1957)]. The first 20 patients received no hemostatic drug, and the last 20 received 25 mg Adona (AC-17) intra-

Table 3 : Bleeding time before and 30 minutes after an intravenous injection of 50 mg Adona (AC-17) in 11 patients with hemorrhagic disorders

Diagnosis	No. of platelets × 1000/cmm	Bleeding time (min)	
		before	after
Leucemia	22	> 30	> 30
Leucemia	47	> 30	> 30
ITP	16	> 30	> 30
Myelomatosis	108	16	18
Cirrhosis of the liver	62	14	15
Aplastic anemia	76	17	11
Unknown*	376	> 30	> 30
Macroglobulinemia	111	19	16
v. Willebrand's disease	268	25	30
v. Willebrand's disease	228	> 30	> 30
v. Willebrand's disease	282	> 30	> 30

* A 73 year old man who acquired a mild bleeding tendency after an acute hepatitis 3 years ago. All clotting factors, platelet adhesiveness to glass, platelet factor 3, and clot retraction were normal. Macroglobulins could not be demonstrated.

Table 4 : Tourniquet test before and 30 minutes after an intravenous injection of 50 mg Adona (AC-17) in 8 patients with bleeding disorders

Diagnosis	No. of platelets × 1000/cmm	Tourniquet test (No. of petecchiae)	
		before	after
Leucemia	22	50—60	50
Leucemia	48	70—90	100
ITP	30	40	25
Myelomatosis	126	80	30—40
Henoch-Schönlein's disease	215	innumerable	innumerable
Henoch-Schönlein's disease	245	innumerable	innumerable
v. Willebrand's disease	260	innumerable	innumerable
v. Willebrand's disease	233	80—100	80

venously prior to operation, and another 25 mg mixed with glucose-saline within the first 2 hours after the operation. The entire study was completed within 3 months, and there was no change in technique during this time. The age distribution was the same in the two groups, and the groups were identical in all relevant respects except for the treatment with Adona (AC-17).

The blood loss during operation and on each postoperative day was measured as hemoglobin in a Klett-Summerson photoelectric colorimeter, and this value was converted to ml of blood by means of the patient's hemoglobin value. Suction was used extensively during the operation, and the blood was collected in a suction bottle. The content of this bottle was diluted with distilled water to 10 liters and the hemoglobin concentration was measured. The swabs used were soaked in water, and the amount of hemoglobin was determined. The 24-hour urine was collected separately for each of the first 3 days, and the hemoglobin was measured. In this way it was possible to measure the entire blood loss over the first postoperative days.

The drug gave the urine a strong yellowish colour, but this did not interfere with the hemoglobin determination.

Table 5 : Blood loss during prostatectomy in 20 patients who received 25 mg Adona (AC-17) intravenously prior to operation and 25 mg in glucose-saline during the first 2 hours postoperatively, compared with a similar group of 20 patients not receiving Adona (AC-17)

Control group

Blood loss in ml

	During operation	Rest of first day	Second day	Third day	Average total blood loss
Mean	141	122	47	40	350
Median	129	94	22	25	
Range	24—286	9—471	6—200	4—154	
Adona (AC-17) group					
Mean	114	163	63	44	384
Median	86	163	45	33	
Range	50—298	32—418	12—166	0—172	

Table 5 shows the blood loss in both groups. The patients receiving Adona (AC-17) bled less during the operation, but more during the rest of the first postoperative day. On the second and third day the blood loss was about the same in the two groups. The average total blood loss did not differ markedly in the two groups.

Clinical impression

We include the following observations reluctantly, since they can *not* be listed as scientific evidence. However, it has not been feasible to collect an ade-

quate control group, and we feel that it would be unfair to leave out these observations, even if clinical impressions may easily be misleading.

4 patients developed a severe gastro-intestinal bleeding after having been dialyzed in an artificial kidney. The surgeon in charge of the patients had tried transfusions and cortisone without any effect on the bleeding. The patients received 25 mg Adona (AC-17) intravenously several times a day. The effect appeared to be marked in 1 patient and probable in the 3 others.

Discussion

In normal individuals we have demonstrated a probable effect of Adona (AC-17) on the tourniquet test, and a possible effect on the bleeding time. The blood loss during the bleeding time test was reduced by one third. This loss depends to a great extent (much more than the bleeding time itself) on the depth of the cut, and it is therefore difficult to evaluate this observation. However, we made the cuts as uniform as possible, and the finding may be of some importance.

We have furthermore shown, in agreement with B u r k e et al. (1960), that Adona (AC-17) given preoperatively reduced the blood loss during prostatectomy. Possibly, the blood loss could have been reduced also after the operation with repeated injections.

In patients with well-recognized hemorrhagic disorders, Adona (AC-17) had no effect on the bleeding time or the tourniquet test. This was, however, to be expected, since the drug has no effect on the platelets or the coagulation system.

Every attempt to find effective, non-toxic hemostatic agents must be welcomed. We have confirmed that Adona (AC-17) is nontoxic, and our findings suggest a hemostatic effect in normals and in patients undergoing prostatic surgery. It is unlikely, however, that the latter effect is of such an order of magnitude that the drug should be used routinely in such operations.

In spite of recent advances, there are still some patients who bleed severely without known causes. These patients may have a serious underlying disease, and therapy with transfusions, cortisone or ε-ACA may have no effect. Our limited experience, based on clinical impressions, suggests that Adona (AC-17) may be of value in such patients.

From this study, it appears unlikely that Adona (AC-17) should be used in the treatment of hemostatic disorders due to platelet or coagulation disorders. However, it *may* be of value in a small group of patients with ill-defined, presumably vascular diseases, who have failed to respond to other therapy.

Summary

In normal individuals 50 mg Adona (AC-17) intravenously increased capillary resistance, and slightly shortened the bleeding time. No effect was observed on coagulation or platelets.

In patients undergoing prostatic surgery the drug *seemed* to reduce the blood loss during the operation.

50 mg Adona (AC-17) was given to 11 patients with a prolonged bleeding time of various causes, and to 8 patients with a positive tourniquet test. No effect could be demonstrated. However, the drug *may* be of value in some patients with acquired, ill-defined, presumably vascular diseases.

Résumé

Chez l'individu normal l'administration intraveineuse de 50 mg d'Adona (AC-17) augmente la résistance capillaire et raccourcit le temps de saignement. L'adona n'a aucun effet sur la coagulation ou les plaquettes.

Le médicament semble réduire la perte de sang chez les malades opérés de la prostate.

50 mg d' Adona administrés à 10 patients ayant un temps de saignement prolongé (causes diverses) et à 8 patients ayant un test du lacet positif n'ont eu aucun effet. Cependant le médicament pourrait avoir quelque valeur dans le traitement de patients souffrant de maladies mal définies probablement d'origine vasculaire.

Zusammenfassung

50 mg Adona (AC-17) i.v. steigerte bei Normalpersonen die Kapillarresistenz und verkürzten die Blutungszeit geringfügig. Es konnte keine Wirkung auf Blutgerinnung und Thrombozyten gefunden werden.

Bei Patienten mit Prostataoperationen schien das Medikament den Blutverlust während der Operation zu vermindern.

50 mg Adona (AC-17) wurden bei 11 Patienten mit aus verschiedenen Gründen verlängerter Blutungszeit und bei 8 Patienten mit positivem Stautest verabreicht. Es konnte keine Wirkung nachgewiesen werden. Das Medikament könnte aber dennoch bei Patienten mit schlecht definierten, vermutlich vaskulären Erkrankungen von Wert sein.

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